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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/510,946	08/08/95	BROW M	FORS-01756

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EXAMINER	
SANDALS,W	

ART UNIT	PAPER NUMBER
1636	18

DATE MAILED: 11/23/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Cpy

Advisory Action

Application No.	Applicant(s)
08/520,946	Lyamichev et al.
Examiner	**Group Art Unit**
First Last	1234

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☐ expires _____ months from the mailing date of the final rejection.

b) ☒ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due two months from the date of the Notice of Appeal filed on _____ (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *Nov 6, 1998* **has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:**

☒ The proposed amendment(s):

☐ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☒ will not be entered because:

☐ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

☐ Applicant's response has overcome the following rejection(s):

_____

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:
please see the accompanying response.

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: _____

Claims objected to: _____

Claims rejected: *1, 3-29, and 31-54*

☐ The proposed drawing correction filed on _____ ☐has ☐has not been approved by the Examiner.

☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ .

☐ Other

DETAILED ACTION

Specification

1. A substitute specification, or substitute pages, excluding claims is required pursuant to 37 CFR 1.125(a) because 186 amendments on 88 pages have been submitted in Paper No. 17, filed November 6, 1998 and constitute an unreasonable burden on the Office to enter into the specification.

A substitute specification, or substitute pages, filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

Response to Amendment

2. The declaration of Mary Ann D. Brow under 37 CFR 1.132 filed November 6, 1998 is insufficient to overcome the rejection of claims 1, 3-29 and 31-54 based upon 35 USC 103(a) as set forth in the last Office action and will be discussed in the body of the repeated rejection below.

Response to Arguments

3. Applicants have submitted amendments to the claims in Paper No. 17, filed on November 6, 1998 which are not found persuasive. Arguments have been set forth which claim that the amendments to claims 1, 5, 7-10, 19 and 44 have provided a distinction over the cited prior art of record. The rejection of claims 1, 3-29 and 31-54 are repeated below, and response to applicants arguments appear within the body of the rejection.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3-29 and 31-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyamichev et al. in view of Young, Seela and Roling, and Young et al.

The claims are drawn to a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus,* wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Also, the microorganism may be virus which may be selected from the group comprising hepatitis C virus (HCV) and simian immunodeficiency virus (SIV). The microorganisms are identified by

cleaving the isolated nucleic acid of the microorganisms where the nucleic acid is treated to form intra-strand secondary cleavage structures. The cleavage structures are cleaved with a cleavage means. The cleavage means may be an enzyme, which may be a nuclease, which may be selected from the group consisting of "Cleavase BN", *Thermos aquaticus* DNA polymerase, *Thermus thermophilus* DNA polymerase, *Escherichia coli* E.O. III, and the *Saccharomyces cerevisiae* Rad1/Rad10 complex. The nucleic acid may comprise a nucleotide analog. The nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. The isolated nucleic acid may be a polymorphic locus which may be isolated by polymerase chain reaction (PCR). The PCR may be done with a nucleotide analog which may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus, which may be ribosomal RNA, which may be 16S ribosomal RNA.

Lyamichev et al. (see entire reference) taught a method for cleaving an isolated nucleic acid where the nucleic acid was treated to form (secondary) cleavage structures. The cleavage structures were cleaved with a cleavage means. The cleavage means was an enzyme, which was a

nuclease, which was selected from the group consisting of *Thermos aquatics* (Tac) DNA polymerase and *Thermos thermophilous* (Tth) DNA polymerase. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of reference nucleic acid structures. The isolated nucleic acid may be a polymorphic locus which may be isolated by polymerase chain reaction (PCR). The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus. Lyamichev et. al. taught that this method can be used to optimize allele-specific PCR. The polymerase was also taught to be a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid.

Lyamichev et al. did not teach a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus,* wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Lyamichev et. al. also did not teach that the microorganism may be a virus which may be selected from the group comprising hepatitis C virus and simian immunodeficiency virus. The reference did not teach that the detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. Lyamichev et al. did not teach that the

nucleic acid may comprise a nucleotide analog, where the nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The reference did not teach that the PCR may be done with these nucleotide analogs or that the PCR primers were from ribosomal RNA, which may be 16S ribosomal RNA.

a- Applicants have argued that the addition of the limitation to the claims that the structure of the nucleic acid substrate form one or more intra-strand secondary structures, where the cleavage means reacts with the intra-strand secondary structures is a distinguishing limitation. Lyamichev et al. taught at page 779, column 1, and at page 781, column 3, that a primer was not required for cleavage, and that the enzyme could recognize and cleave intra-strand secondary structures. It is noted that the declaration of Mary Ann D. Brow, filed November 6, 1998 accurately states that Lyamichev et al. taught that a primer was necessary for cleavage of RNA. This is not sufficient to distinguish the instant claims over the prior art because the instant claims recite a *nucleic acid.* Amending the claims to limit the invention to RNA may provide a patentable distinction.

b- It is also argued that cleavage specificity and efficiency is improved by the instant claimed invention over the teachings of Lyamichev et al. These limitations are not claimed and may provide patentable distinction over the prior art.

Young (see especially columns 3-4 and 10) taught the use of PCR with the nuclease *Thermos aquaticus* (Tac) DNA polymerase to identify the polymorphic loci of ribosomal 16S RNA from *Mycobacterium spp.* which increased the speed, accuracy and sensitivity of detection

of disease causing microorganisms which were difficult to culture and could take up to several weeks to identify by culture methods.

Seela and Roling (see especially pages 55 and 61) taught the use of 7-deaza-dATP, 7-deaza-dGTP and dUTP in PCR reactions. The use of these nucleotide analogs helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions.

Young et al. (see especially the introduction) taught the use of PCR with the nuclease *Thermos thermophilous* DNA polymerase for the detection of hepatitis C virus (HCV) in clinical diagnostics, which was an effective means of direct detection of HCV that streamlined the procedure, reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increased specificity of the primer extension.

c- Applicants have argued that Young, Seela and Roling and Young et al. do not teach the cleavage of intra-strand secondary structures in nucleic acids. This is true. These references are relied upon here to teach obvious methods which are well known in the art, which have been included as claimed limitations to the base invention which is taught by Lyamichev et al. These teachings are provided to demonstrate that the claimed limitations are merely adaptations of well known methods.

It would have been obvious to combine the teachings of Lyamichev et al. with Young, Seela and Roling, and Young et al. to produce a method for identifying strains of microorganisms, which may be bacteria or viruses, where the microorganisms were identified by cleaving the

isolated nucleic acid which was treated to form (secondary) cleavage with a nuclease because Lyamichev et. al. taught that this method could be used to optimize allele-specific PCR. The polymerase was also taught to be a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid. Seela and Roling recited the use of Tac polymerase with nucleotide analogs 7-deaza-dATP, 7-deaza-dGTP and dUTP in PCR reactions and taught that the use of these nucleotide analogs would have helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions. Young et. al. taught the use of PCR with the nuclease *Thermos thermophilous* DNA polymerase for the detection of hepatitis C virus (HCV) in clinical diagnostics. They taught that the use of Tth DNA polymerase in PCR was an effective means of direct detection of HCV which streamlined the procedure and reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increasing the specificity of the primer extension.

One of ordinary skill in the art would have been motivated to combine the teachings of Lyamichev et al. with Young, Seela and Roling, and Young et al. to produce a method that could be used to optimize allele-specific PCR wherein the polymerase is also a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid because Lyamichev et. al. taught that this method could be used to optimize allele-specific PCR. Lyamichev et al. also taught that the polymerase was a single stranded endonuclease which recognized hairpin structures. Seela and Roling taught the method using Tth DNA polymerase or

Tac DNA polymerase which incorporated nucleotide analogs 7-deaza-dATP, 7-deaza-dGTP and dUTP in PCR reactions demonstrating that the use of these nucleotide analogs helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems which are frequently encountered in polymerase reactions. Also, the use of nuclease *Thermos thermophilous* DNA polymerase in PCR assays was an effective means of direct detection of HCV as taught by Young et al. because it streamlined the procedure and reduced potential contamination of the reaction by eliminating the addition of a second enzyme which also increased the specificity of the primer extension. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Lyamichev et al., Young, Seela and Roling, and Young et al.

Conclusion

6. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.

Examiner

November 19, 1998

JAMES KETTER
PRIMARY EXAMINER